PATENT

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December 14, 2000
Date

Carol E. Williams

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Douglas J. Jolly et al.
Application No.	:	09/001,039
Filed	:	January 13, 1998
For	:	METHODS FOR ADMINISTRATION OF RECOMBINANT GENE DELIVERY VEHICLES FOR TREATMENT OF HEMOPHILIA AND OTHER DISORDERS
Examiner	:	Robert Schwartzman
Art Unit	:	1636
Docket No.	:	930049.441C4
Date	:	December14, 2000

Box AF
Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER AMENDMENT

I, Douglas J. Jolly, hereby declare that:

1. I am a joint inventor of the subject matter of claims 1-3 and 57 as presently pending in U.S. Patent Application No. 09/001,039, filed January 13, 1998 ("the claimed invention").

2. I am presently employed by Chiron Corporation (hereinafter "Chiron"), the assignee of the above-identified patent application.

3. I have reviewed the Examiner's Office Action dated June 14, 2000 (Paper No. 17), in particular the section entitled "Claim Rejections - 35 U.S.C. § 103" starting

on p. 4. The Examiner for this invention indicates (1) that claims 1-3 may be rejected under 35 U.S.C. § 103(a) over Mulligan et al., U.S. Patent No. 5,674,722 (filed May 25, 1994) in view of either Mason et al., U.S. Patent No. 5,643, 770 (filed July 21, 1994) or Takeuchi et al., *J. Virol.* 68:8001-8007 (December, 1994) and (2) that claim 57 may be rejected under 35 U.S.C. § 103(a) over Kay et al., *Science* 262:117-119 (1993) in view of either Mason or Takeuchi.

4. In order to assist the Examiner in evaluating of patentability of claims 1-3 over the cited references, I am providing the following remarks showing that the present invention was conceived prior to the publication date of the Mulligan, Mason, and Takeuchi references (*i.e.* prior to May 25, 1994) and that this invention was diligently reduced to practice, culminating in the filing of the co-pending U.S. Patent Application No. 08/367,071 (the '071 Application) from which application the present application claim benefit.

5. As evidence of the conception of the claimed invention, followed by a reduction to practice thereof, I have reviewed a laboratory notebook prepared by Caterine DeJesus a non-inventor working under the direction of Nicholas DePolo, a co-inventor in the claimed invention. In addition, I have reviewed monthly reports based on work performed prior to May 25, 1994. From these reports, I conclude that we conceived the replication defective recombinant retroviruses of instant claims 1-3 prior to May 25, 1994 and that the invention of claims 1-3 was diligently pursued up to the filing date of co-pending U.S. Patent Application No. 08/367,071 (the '071 application), filed December 30, 1994.

6. The '071 Application discloses the preparation of various replication defective recombinant retroviruses comprising a human factor VIII coding region. For example, Example 2 discloses the production of pJW-2 by subcloning the cDNA sequence encoding factor VIII from pCIS-F8 into the replication defective retroviral vector pKT-1. Similarly, Example 2 discloses the preparation of a family of alternative replication defective retroviral vectors encoding factor VIII derived from pCIS-F8 wherein a portion of the 3' untranslated region was removed. The resulting vectors were

named pKT-ND2, pKT-ND3 and pKT-ND5. Each of these replication defective retroviral vectors encode the full-length factor VIII protein.

7. The '071 Application also discloses the preparation of replication defective recombinant retroviruses comprising B domain-deleted forms of factor VIII. For example, Example 2 discloses the preparation of the replication defective recombinant retrovirus B-del-l which retroviral vector was prepared by subcloning a cDNA encoding a B deleted factor VIII from plasmid vector p25D into the replication defective recombinant retrovirus vector JW-2.

8. The '071 Application further discloses that replication defective recombinant retroviruses comprising various wild-type and B domain-deleted forms of factor VIII effectively express factor VIII protein when transfected into various mammalian cell lines such as, *e.g.*, the murine L33 cell line. More specifically, Example 2(B)(l) discloses that supernatant harvested from L33 cells transfected with KT-ND5 express factor VIII protein as determined by assaying by the COATEST® Factor VIII assay (KabiVitrum Diagnostica, Molndal, Sweden). Similarly, Example 2(B)(2) discloses that supernatant harvested from the human cell line JY-KT-ND5 also contained factor VIII expressed off the KT-NT5 replication defective retroviral vector.

9. The '071 Application (Example 2(F)) also shows that retroviral particles obtained from both human (HX and HA) and canine (DX and DA) packaging cell lines, transfected with KT-ND5, are capable of infecting the human cell line HT1080. Furthermore, factor VIII was detected by the COATEST® Factor VIII assay in supernatants harvested from the HX-KT-ND5 infected HT1080 cells.

10. The '071 Application, Example 11(A), further shows that retrovirus containing supernatants from human embryonic kidney cell line 293-derived packaging cells (2A and 2X) were resistant to human complement mediated serum inactivation whereas retrovirus containing supernatants from canine D17-derived packaging cell lines (DA and DX) were sensitive to human complement mediated serum inactivation. Moreover, retrovirus derived from human packaging cells was progressively more

sensitive to chimpanzee, baboon and macaque complements, respectively, in order of increasing phylogenetic distance from human (Example 11(B)). Example 11 also disclosed that similar results were obtained with alternative recombinant retrovirus packaged in DA and 2A cells as well as in HX (a HT1080-derived packaging cell line).

11. In summary, upon review of the above referenced laboratory notebook and monthly reports, I conclude that prior to May 25, 1994, we conceived of preparing the replication defective recombinant retroviruses of instant claims 1-3. Moreover, prior to May 25, 1994, we diligently pursued and reduced to practice the replication defective recombinant retroviruses provided by claims 1-3. Accordingly, we respectfully submit that none of the Mulligan, Mason or Takeuchi references is not prior art as to any of these claims.

12. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and correct. Further, the undersigned understands that willful, false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Dated: _____

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DOUGLAS J. JOLLY